REMARKS/ARGUMENTS

Claims 7-19 and 21 remain in this application. Claims 7, 9-12, 14 and 16-19 have been amended.

I. The Rejection Under 35 U.S.C. § 112, Second Paragraph

The final Office Action rejects claims 14-16 as confusing. In response, Applicants amend claim 14 in accordance with the final Office Action's suggestion to obviate the rejection. Support for the amendment can be found in the specification at, e.g., page 7, lines 1-7. Reconsideration and withdrawal of the rejection are respectfully requested.

II. The Rejection Under 35 U.S.C. § 112, First Paragraph

The final Office Action rejects claims 7-21 under 35 U.S.C. § 112, first paragraph. In particular, the final Office Action asserts the following:

(1) that "neither the claims nor the specification teach that the inhibitor of the truncated form of aggrecanase inhibits also the wild type (full length?) enzyme";

(2) that the truncated forms of aggrecanase disclosed in the specification cannot degrade aggrecan; in particular that:

> On page 1 and 2 of the specification Applicants define two species of the genus aggrecanase, i.e. ADAMTS-4 and ADAMTS-5 as Aggrecanase–1... and Aggrecanase-2... wherein both enzymes cleave the site Glu373-Ala374 in the interglobular domain of aggrecan.
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> On page 2 under the subtitle "Summary of the Invention" the term Aggrecanase-1 is defined as the polypeptide SEQ ID NO: 8, consisting of amino acids 1-447, of which amino acids 1-437 are identical to amino acids 1-437 of aggrecanase-1, ADAMTS-4 (NM 005099). In the same passage of the specification the term Aggrecanase-2 means the polypeptide of SEQ ID NO: 9 consisting of 1-492 amino acids of which amino acids 1-482 are identical to amino acids 1-482 of ADAMTS-5 (11) (NM 007038). *According to teachings of Abbaszade I. et al., see the enclosed Fig. 1, ADAMT-4 and –11 truncated to contain only 437 and 482 N-terminal amino acids do not contain disintegrin-like domains and trombospondin motifs that are crucial for degradation of aggrecan...*

See pages 5-6.

(3) that "[n]ot all peptides disclosed by Applicants are substrates for both SEQ ID NO: 8 and 9...";

(4) that the term "wild type aggrecanase" constitutes new matter;

(5) that the claimed genus of peptides that are less than 40 amino acids in length and that contain a cleavage site between a glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acid residue on the C-terminal side is "insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus... [a]pplicants themselves did not disclose all possible peptides that are less than 40 amino acids long and are the substrates of all full length, partial, truncated, chimeric or modified aggrecanases";

(6) that "[a]pplicants fail to disclose any particular structure to function relationship identifying the genus of truncated polypeptides to be used in the claimed methods"; and

(7) that "the specification... does not reasonably provide enablement for methods to detect compounds that inhibit any wild type aggrecanase (full length aggrecanase) using any peptide less than 40 amino acids in length comprising a cleavage site for any truncated aggrecanase wherein said site is located between a glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acids residues on the C-terminal side polypeptides.

Applicants respectfully traverse the rejection. Applicants respectfully submit that the subject matter of claims 7-21 is clearly disclosed in the present specification. Applicants will address the (7) enumerated points above herein.

In response to (1), the specification discloses that the peptide substrates of the invention were identified as compounds that are capable of being cleaved by the truncated forms of aggrecanase-1 and aggrecanase-2 disclosed in the specification, i.e., SEQ ID NO:8 and SEQ ID NO:9 (see, e.g., page 5, lines 1-10, and Figs. 2-4B). The ability to modulate the enzymatic activity of the truncated aggrecanases demonstrates an ability to modulate full-length aggrecanase. The specification discloses therefore that the truncated aggrecanases and peptide substrates of the invention can be used in high throughput screening to identify modulator compounds for further assay.

> It has been demonstrated that aggrecanase cleavage sites in aggrecan contain glutamic acid on the N-terminal side of the cleavage site (P1 position) and a non-polar or uncharged residue on the C-terminal side of the cleavage site (P1' position), namely alanine, leucine or glycine [citation omitted]. As shown later under Kinetic Analysis in Example 2, the truncated aggrecanase-2 used in the assays described here cleaves the peptides of SEQ ID NOS: 3 and 4 between glutamic acid and leucine residues, consistent with the cleavage specificity of aggrecan cleavage sites.

See page 8, lines 20-29.

In response to (2), Applicants themselves recognize that the disintegrin-like domains and tromobospondin motifs play a role in aggrecan degradation. Namely, Applicants disclose that:

> The term "truncated aggrecanase" as used herein refers to a **truncated enzyme (as shown in Fig. 1) that displays enzymatic cleavage of a peptide substrate, and for which the corresponding full-length enzyme is known to have the capacity to cleave aggrecan**. Efficient cleavage of aggrecan depends on multiple interactions between the enzyme and aggrecan. For example, cleavage depends on an intact N-terminal portion of the substrate, aggrecan [citation omitted]. **Tortorella et al. (J. Biol. Chem. 275:25791-25797, 2000) showed that cleavage of aggrecan was dependent on the thrombospondin motif in the enzyme, aggrecanase-1, although both full-length and truncated aggrecanase-1 could cleave a peptide substrate (quoted as unpublished data).**[1]

See page 7, line 32 to page 8, line 7. Regardless, Applicants' invention lies in the fact that the truncated aggrecanases and peptide substrates of the invention can be employed in high-throughput screening to identify modulator compounds for further assay. Thus, Applicants have shown that both full-length and truncated aggrecanase could cleave the peptide substrates provided that the peptide substrates contain the aggrecanase-sensitive cleavage site.

In response to (3), Applicants have identified two peptide substrates that would be particularly useful in high throughput screening. Applicants believe that additional peptide substrates may also prove useful. The attributes of such peptide substrates are defined in response to (5) below.

In response to (4), those of ordinary skill in the art would readily appreciate that the "wild type" form of an enzyme is the naturally occurring or "full-length" form of the enzyme. The claims have been amended to include language specifically employed in the specification in accordance with the final Office Action's suggestion.

In response to (5), the attributes and features of all species within the claimed genus include: (i) amino acid sequence; (ii) less than 40 amino acids in length; (iii) containing a cleavage site between a glutamic acid on the N-terminal side of the cleavage site and a non-

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[1] "In addition, both the full-length and truncated aggrecanase-1 cleaved a peptide substrate containing the aggrecanase-sensitive cleavage site, NITEGE-ARGS." Cited in Tortorella et al. (2000) as M. D. Tortorella, R.-Q. Liu, and E. C. Arner, unpublished data.

polar or uncharged amino acid residue on the C-terminal side; and (iv) are capable of being cleaved by the inventive metalloprotease enzyme's of the invention.

In response to (6) as discussed above, the truncated enzymes of the invention are defined in the specification as those truncated enzymes: (i) that display enzymatic cleavage of a peptide substrate defined according to the invention; (ii) for which the corresponding full-length enzyme is known to have the capacity to cleave aggrecan; and (iii) that contain the metalloprotease domain.

In response to (7), the assay of the invention provides methods to screen for compounds that inhibit the truncated aggrecanase-1 and aggrecanse-2. The identified compounds can be employed in additional assays to determine the effect on full-length enzyme.

Reconsideration and withdrawal of the rejection of claims 7-21 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Early consideration and prompt allowance of the pending claims are respectfully requested.

Respectfully submitted,

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